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Usefulness of plasmapheresis in patients with severe complicated thyrotoxicosis

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ABSTRACT

The standard treatment of complicated thyrotoxicosis and thyroid storm with the concomitant use of antithyroid medication, iodine, beta-blockers, and corticosteroids is successful in most cases. However, treatment options are limited when antithyroidal drugs cannot be used or in cases that are refractory to standard treatment. Plasmapheresis provides a safe and effective strategy when initial treatment fails, facilitating the transition to definitive treatments such as thyroidectomy. We present two adults with complicated thyrotoxicosis successfully treated with plasmapheresis as a bridge therapy to thyroidectomy or as an alternative to drug-induced toxicity.

KEYWORDS Plasmapheresis; thyroid storm; thyrotoxicosis; tissue plasma exchange

Thyroid storm is an acute complication of thyrotoxicosis that requires immediate and aggressive treatment to avoid its devastating consequences.[1] Management strategies include measures to reduce thyroid hormone synthesis and release, inhibit the conversion of thyroxine (T4) to triiodothyronine (T3), and decrease the peripheral effects of excess thyroid hormone at the tissue level.[2,3] The use of plasmapheresis has been reported in refractory cases when conventional therapy is not successful or not feasible,[4] but no clear consensus exists regarding its role in the treatment of thyrotoxicosis, and data regarding its safety and effectiveness are scarce.

CASE DESCRIPTIONS

Two adults with complicated thyrotoxicosis were successfully treated with plasmapheresis as a bridge therapy to thyroidectomy or as an alternative to drug-induced toxicity *(Table 1)*. The first patient had a complicated hospital course and was admitted to the intensive care unit in atrial fibrillation with rapid ventricular response refractory to medical and electrical cardioversion. She developed respiratory distress and required endotracheal intubation and vasopressor support. A transthoracic echocardiogram revealed an ejection fraction of 30% to 35% with global hypokinesis. A temporary left ventricular assist device (Impella) was placed and removed 24 hours later due to a remarkable improvement in her ejection fraction to 50% to 55%. Standard medical therapy for thyroid storm was initiated; however, the patient's hemodynamic compromise and tachyarrhythmia persisted. Given that her hyperthyroid state was refractory to medical treatment, she was started on plasmapheresis on day 10 of hospitalization with a significant reduction in serum free T4 and free T3 levels *(Figure 1)*, remarkable improvement in hemodynamic status, and complete resolution of tachycardia. In contrast, our second patient had a milder case of thyrotoxicosis with concomitant cardiomyopathy. An echocardiogram showed an ejection fraction of <20% with severe global hypokinesis of the left ventricle and diastolic dysfunction. Forty-eight hours after initiating treatment with propylthiouracil, he developed altered mental status and

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Table 1. Clinical features of hyperthyroid patients who underwent plasmapheresis

Variable	Case 1	Case 2
Demographics	51-year-old white woman	64-year-old black man
Past medical history	Untreated subclinical hyperthyroidism, hypertension	Untreated Graves' disease, tachycardia-induced cardiomyopathy
Presenting symptom	Sudden onset of shortness of breath, palpitations, agitation	3-week history of fatigue, GI symptoms, tremors, heat intolerance
Vital signs	Atrial fibrillation with RVR (HR 140 bpm), tachypnea (RR 40 bpm), normotensive, afebrile	Sinus tachycardia (HR 114 bpm), hypertensive (BP 160/80 mm Hg), afebrile
Thyroid function tests	TSH 0.006 mUI/mL, FT4 1.62 ng/dL, undetectable TSI and TPO antibodies, TSI 0.89 (≥140%), TPO <9 IU, thyroglobulin 2100 ng/dL	Suppressed TSH, FT4 > 7.77 ng/dL, FT3 28 pg/mL
Diagnostic tests/workup	Chest CTA, cardiomegaly with bilateral effusions and diffuse alveolar infiltrates, no pulmonary emboli; thyroid ultrasound, right thyroid nodule 5.0 × 2.2 × 3.7 cm	Aspartate transaminase 17 U/L, alanine transaminase 21 U/L, alkaline phosphatase 131 IU/L, total bilirubin 0.6 mg/dL
JTA criteria	Definite thyroid storm	Suspected thyroid storm
BWPS	45	30
Apache II	22	14
Management	**Atrial fibrillation with RVR:** diltiazem, esmolol and amiodarone infusions, digoxin, electrical synchronized cardioversion **Acute hypoxemic respiratory failure:** mechanical ventilation **Cardiogenic shock:** vasopressor and Impella support **Thyrotoxicosis:** maximum doses of propranolol, hydrocortisone, PTU, cholestyramine, iodine	**Thyrotoxicosis:** PTU, potassium iodine, hydrocortisone, propranolol, cholestyramine **Liver toxicity:** Discontinuation of PTU, initiation of methimazole
Plasmapheresis	Five sessions starting on hospital day 10	One session
Outcome	Total thyroidectomy on day 16 without complications	Normalization of mental status and improvement of liver enzymes

APACHE II indicates Acute Physiology and Chronic Health Evaluation II score; BP, blood pressure; BWPS, Burch-Wartofsky Point Scale; CTA, computed tomography angiography; FT3, free triiodothyronine; FT4, free thyroxine; GI, gastrointestinal; HR, heart rate; JTA, Japanese Thyroid Association; PTU, propylthiouracil; RR, respiratory rate; RVR, rapid ventricular rate; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating antibodies.

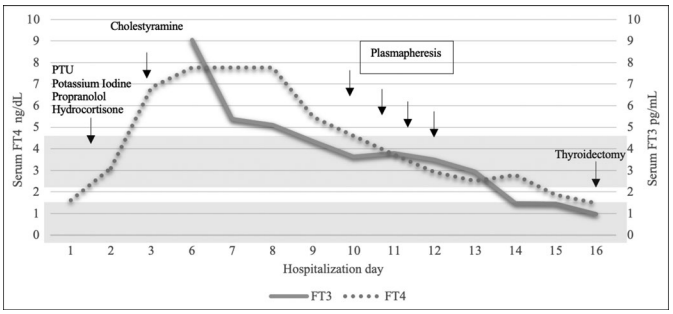

Figure 1. Thyroid hormone levels during hospital stay. Treatment included oral potassium iodine, cholestyramine, hydrocortisone, and propylthiouracil. In this hospital, the normal range for free thyroxine (FT4) is 0.93 to 1.7 ng/dL and for free triiodothyronine (FT3), 2.3 to 4.2 pg/mL, as highlighted in the graph. The patient had five sessions of plasmapheresis as indicated by the arrows.

acute liver toxicity. Propylthiouracil was discontinued, and he underwent one session of plasmapheresis with normalization of his mental status and improvement in his liver enzymes.

DISCUSSION

The reported cases illustrate that plasmapheresis is a rapid, safe, and lifesaving therapeutic alternative when there is a poor response to medical management or when drug toxicity hinders its use. In the first case, plasmapheresis was implemented for persistent hemodynamic instability despite maximized medical management, with improvements in both clinical status and hormonal levels after five sessions. In the second case, propylthiouracil-induced hepatotoxicity led to the use of plasmapheresis with rapid resolution of encephalopathy and reduction in liver enzymes. Our cases illustrate that plasmapheresis is an excellent option in those patients with rapid clinical deterioration, treatment failure, or need for emergent thyroidectomy.

The prevalence of hyperthyroidism in the United States is 1.3%; thyroid storm occurs in 0.22% of all thyrotoxic patients, with an overall mortality of 8% to 30%.[5] Treatment strategies include thionamides, iodine solution, bile acid sequestrants, hydrocortisone, and beta-adrenergic receptor blockers *(Figure 2)*.[2] Minor side effects of thionamides occur

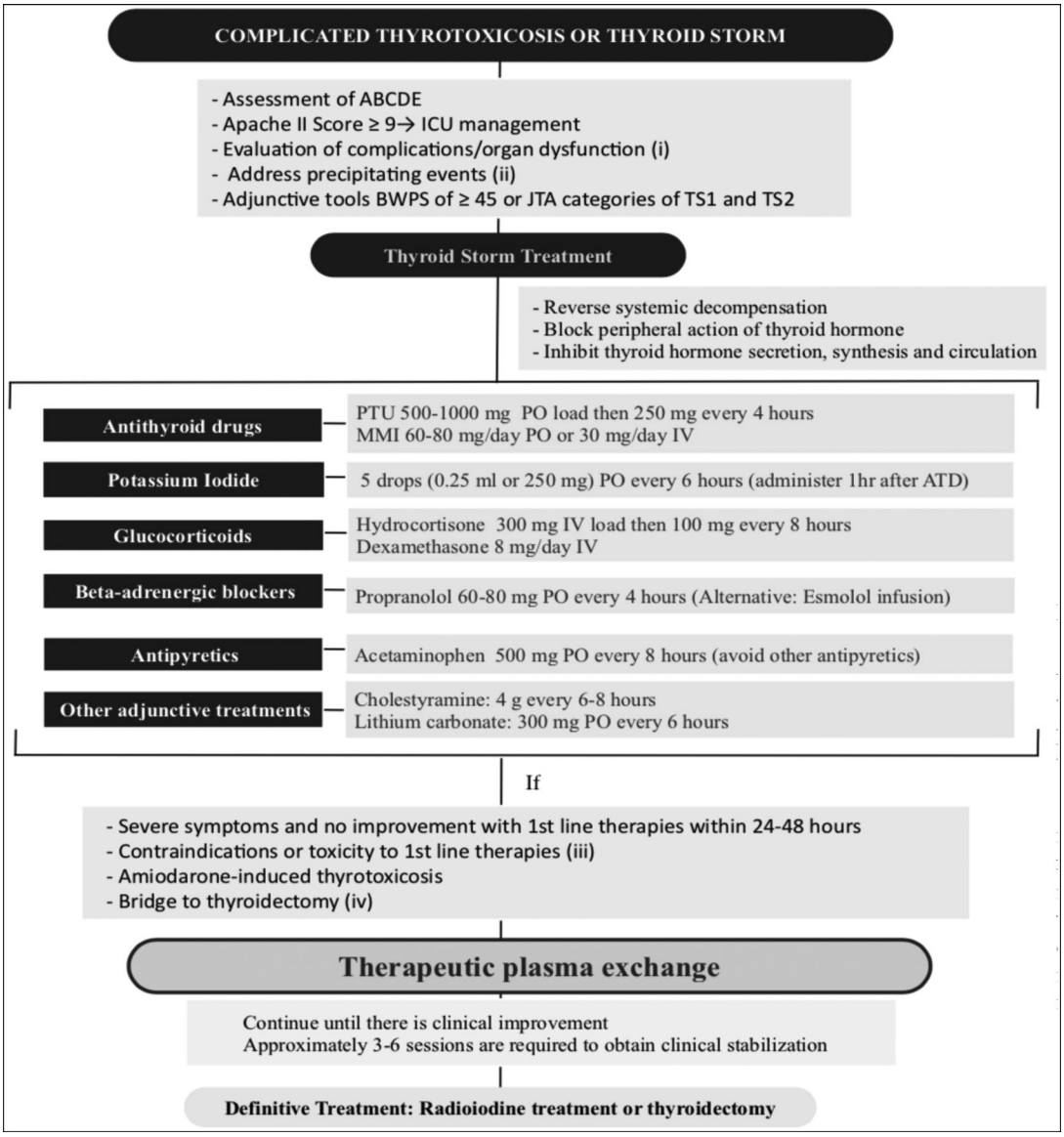

Figure 2. Algorithm for the management of complicated thyrotoxicosis or thyroid storm. Notes: (i) Complications include acute liver failure, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, and acute respiratory distress syndrome. (ii) Precipitants include abrupt discontinuation of antithyroid medications, amiodarone-induced thyroid storm, infection, trauma, thyroidal and nonthyroidal surgery, radiation thyroiditis, diabetic ketoacidosis, use of tyrosine-kinase inhibitors, and excess iodine in hyperthyroid patients. (iii) Examples include acute liver failure and agranulocytosis associated with antithyroid drugs. (iv) Therapeutic plasma exchange allows a thyrotoxic patient to reach a euthyroid state prior to thyroidectomy. ABCDE indicates airway, breathing, circulation, dysfunction of central nervous system, exposure and environmental control; APACHE II, Acute Physiology and Chronic Health Evaluation II; ATD, antithyroid drugs; BWPS, Burch-Wartofsky Point Scale; ICU, intensive care unit; IV, intravenous; JTA, Japanese Thyroid Association; MMI, methimazole; PO, oral; PTU, propylthiouracil; TS1, thyroid storm 1 definite; TS2, thyroid storm 2 suspected. Figure created by the authors based on Idrose 2015,[19] Padmanabhan et al 2019,[14] Ross et al 2016,[10] and Satoh et al 2016.[18]

in about 5% of patients and include pruritus, arthralgia, and gastrointestinal distress.[6,7] Agranulocytosis is a rare but life-threatening side effect and generally occurs within 90 days after initiation of therapy.[8] Hepatotoxicity occurs in 0.1% to 0.2% of patients, mainly in the first 3 months of therapy, and most commonly presents as hepatitis. Acute liver failure is rare and is more frequently associated with propylthiouracil.[9,10]

Patients who do not respond to standard therapy and in whom the effects of severe thyrotoxicosis persist despite medical management may warrant emergent thyroidectomy,[2,3,7,10] for which an euthyroid state is preferable prior to surgical intervention to achieve better results.[11] Alternative measures should be used as a bridge for urgent thyroidectomy. Plasmapheresis involves the extracorporeal separation of plasma from the blood. By using the centrifugation technique, plasma is separated from the cellular components of the blood and discarded. Later, cellular components are returned to the patient along with replacement fluid, such as plasma, albumin, and crystalloid.[12,13]

Plasmapheresis is a quick and efficient way to remove pathological proteins, including autoantibodies, paraproteins, and cytokines, from the circulation.[14] According to the American Society for Apheresis, it can be considered a therapeutic option in the setting of complicated thyrotoxicosis in patients with severe symptoms and rapid clinical deterioration, failure of conventional therapies, contraindications to other therapies, or multiorgan decompensation.[4,15,16] Additionally, given amiodarone's long half-life, plasmapheresis is used to lower amiodarone plasma concentrations in patients with amiodarone-induced thyrotoxicosis, particularly in those with no underlying thyroid pathology who develop drug-induced destructive thyroiditis.[10,14,17,18]

Data on the use of plasmapheresis for thyrotoxicosis are limited to case series, and it has been shown to decrease the serum total T4 30 times faster than conventional treatment and shorten its half-life from 106.5 ± 44.6 hours to 59.7 ± 20.2 hours ($P < 0.05$).[4] One study reported a total extraction of free T4 and free T3 of 20% to 60% and 20% to 40%, respectively, after three exchanges.[19] Ezer reported 11 cases of severe thyrotoxicosis, in which the use of plasmapheresis preoperatively enabled patients to undergo thyroidectomy safely, with improvement of thyrotoxicosis and good postoperative outcomes.[16]

The American Society of Apheresis recommends sessions every 24 hours to every 3 days until clinical improvement is noted. The incidence of severe and life-threatening complications is approximately 0.025% to 4.75% of all plasmapheresis sessions, but most complications are mild and transient.[19,20] Complications include hypotension, hemolysis, anaphylactic or allergic reactions, coagulopathy, vascular injury, volume-electrolyte shift, and catheter-related infection.[17]

Plasmapheresis should be included in the treatment algorithm for thyrotoxicosis and should be highlighted more when considering treatments for refractory cases, as illustrated in *Figure 2*.

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